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Original Research Article

Profile of retinopathy of prematurity in late preterm newborn in a district level special newborn care unit of Eastern India

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ABSTRACT

Background: The aim of this study was to analyse the incidence, severity and risk factors of retinopathy of prematurity in late preterm newborn at a district level SNCU in eastern India.
Methods: The initial examination was carried out at 3 weeks of postnatal age or at 31weeks of post-conceptional age, whichever was later. Retinopathy was graded into stages and zones as per the ICROP classification. Those who had ROP were examined every week till regression occurred or till they reached criteria for laser treatment which was type I Prethreshold ROP as per ET ROP guideline. Risk factors for the development of ROP were determined by reviewing maternal and perinatal history and hospital case records.
Results: 212 late ptreterm newborn were examined. The incidence of ROP in late preterm was 16.51% (35 out of 212 newborn). Incidence of stage I ROP was 6.60 % (14 newborn had stage I ROP). Incidence of stage II ROP was 6.60% (14 had stage II ROP). None had stage III ROP. 7 had APROP. Incidence of APROP was 3.30 %. 5 out of 14 newborns with stage II ROP (35.71%) required laser treatment. All newborn with APROP required both laser and Anti VEGF treatment. Overall 34.28% of late preterm with ROP required treatment. There was no difference in gestational age and birth weight in late preterm with and without ROP. There was significant difference in the duration of oxygen therapy in late preterm with and without ROP (6.657±2.531days vs 0.694±1.397 days, $p<0.001$). In stepwise logistic regression analysis-use and duration of oxygen, birth asphyxia and anemia were found to be significant risk factors of ROP in late preterm.
Conclusions: ROP is common in late preterm newborn in developing country like India.

Keywords: Aggressive posterior retinopathy of prematurity, Late preterm, Retinopathy of prematurity, Risk factors

INTRODUCTION

Births between 34- and $36^{6/7}$-weeks' gestation (referred as late preterm births) account for approximately 70% of all preterm birth.[1] In recent years incidence of late preterm birth has increased substantially, mostly because of increased use of Assisted reproductive technologies resulting in increased frequency of multifetal gestation and thus premature delivery. Though larger in size than usual premature infants they are still immature and at risk of developing several short- and long-term complications. They have a higher incidence of transient tachypnea of the newborn, respiratory distress syndrome, persistent pulmonary hypertension of the newborn, respiratory failure, jaundice, temperature regulation problems, hypoglycemia, and feeding difficulties than term infants. Less is known about ocular complications of late preterm infant, specially in developing country with suboptimal control of supplementary oxygen and monitoring. Data is emerging about substantial incidence of Retinopathy of prematurity in more mature and bigger infants from India. Jalali S et al in a prospective observational study of

infants who underwent laser treatment or surgery for ROP found that the mean gestational age of infant was 29.6 weeks (range 26 to 36 weeks) with birth weight ranging from 710 gm to 2000 gm.[2]

The facility based newborn care and establishment of district level special newborn care unit (SNCU) all over the country has improved survival of high risk newborns including premature and low birth weight infants especially late preterm. According to the update of WHO in 2014, India accounts for highest number of preterm birth in the world, among 15 million total preterm deliveries globally, 3.5 million birth occurs in India. India is leading among top ten countries with maximum number of late preterm births. The improved survival of preterm infants has exposed the cohort to various complications of prematurity including retinopathy of prematurity.

India is now in a phase of third epidemic of ROP which is characterized by severe ROP in more mature preterm babies due to their increased survival than past along with suboptimal level of care and monitoring.[3] Hence this study has been performed to evaluate the incidence, risk factors, severity and evolution of ROP and APROP in late preterm newborn admitted in the SNCU at M R Bangur hospital, the district hospital of South 24 parganas, West Bengal, India.

METHODS

All late preterm newborn (34 and $36^{6/7}$ weeks' gestation) admitted in SNCU of M. R. Bangur Hospital, West Bengal which also serves as a satellite unit of IPGME and R and SSKM Hospital, Kolkata were routinely screened for ROP from January 2016 to December 2017. Risk factors for the development of ROP were determined by reviewing maternal and perinatal history and hospital case records. The initial examination was carried out at 3 weeks of postnatal age or at 31weeks of post-conceptional age, whichever was later by indirect ophthalmoscopy by ophthalmologist at the ROP clinic of neonatology department, IPGME and R, Kolkata. Retinopathy was graded into stages and zones as per the ICROP classification.[4-6] Those who had ROP were examined every week till regression occurred or till they reached criteria for laser treatment, which was type I Pre-threshold ROP as per ET ROP guideline.[7]

Laser was done by the same Ophthalmologist under topical anesthesia and systemic sedative and analgesic in the NICU of IPGME and R and SSKM Hospital after transporting the baby preferably within 48 hours of diagnosis. If regression was found to be inadequate or skip areas were seen on subsequent examination, laser was repeated. Intravitreal Bevacizumab was given in severe cases of APROP prior to laser treatment. All intervention including laser and intravitreal Bevacizumab therapy were undertaken after obtaining written consent from the parents.

Statistical analysis

Categorical variables were reported as count and percentage and continuous variables as mean±standard deviation (SD). To detect ROP risk factors, authors performed simple and multiple logistic regressions with stepwise method and Odds ratio (OR) with 95% confidence interval (95% CI) were reported. Univariate analysis was conducted using Chi square test and Fischer's exact test, as applicable. Multiple logistic regression analysis was performed to study the predictors of ROP using independent variables among those variables which were significant in the univariate analysis. P-values less than 0.05 was considered as statistical significant. All data analysis was done with IBM SPSS Statistics for Windows (IBM Corp. Released 2011. Version 20. 0. Armonk, NY: IBM Corp).

RESULTS

212 late preterm newborn were examined during the study period. The incidence of ROP in late preterm was 16.51% (35 out of 212 newborn). Incidence of stage I and stage II ROP was 6.60 % each (14 newborn had stage I and another 14 had stage II ROP). None had stage III ROP. Similarly, no stage IV and V ROP were found in present study population. 7 had APROP. Incidence of APROP was 3.30 % (Table 1).

Table 1: Distribution of ROP in different gestation age group.

POG (weeks)	No ROP	ROP	Stage I	Stage II	Stage III	APROP
34	56	19	8	6	0	5
35	51	3	0	2	0	1
36	70	13	6	6	0	1

POG-Period of Gestation, ROP- Retinopathy of Prematurity

Out of 35 late preterm diagnosed with ROP, 12 required treatment (i.e. 34.28% of late preterm with ROP). None of the newborn with stage I ROP required treatment. 5 out of 14 newborn with stage II ROP (35.71%) required laser treatment as per ETROP guideline. All late preterm newborn with APROP (7 newborn) required both laser

and anti VEGF treatment. On further follow up, only 2 newborn with stage II disease did not complete entire ROP screening, rest had regression of ROP including those with APROP.

Table 2: Univariate analysis of risk factors of ROP in late preterm newborn.

Risk factors	With ROP	Without ROP	P value	OR (95% CI)
POG in weeks (mean±SD)	34.82±0.95	35.07±0.84	0.117	
Birth weight in g (mean±SD)	1536.31±292.06	1609.37±240.93	0.115	
Presence of birth asphyxia; n (%)	12 (34.28%)	15 (8.47%)	<0.001	5.634 (2.347-13.527)
Use of oxygen; n (%)	35 (100%)	39 (22.03%)	<0.001	248.949 (14.934-4149.98)
Duration of oxygen therapy (mean±SD)	6.657±2.531	0.694±1.397	<0.001	
Use of packed red blood cell; n (%)	8 (22.85%)	6 (3.38%)	<0.001	8.444 (2.717-26.237)
Presence of anemia; n (%)	8 (22.85%)	6 (3.38%)	<0.001	8.444 (2.717-26.237)
Presence of apnea; n (%)	15 (42.85%)	10 (5.64%)	<0.001	12.525 (4.967-31.581)
Use of phototherapy; n (%)	17 (48.57%)	44 (24.85%)	0.005	2.854 (1.3548-6.015)
Presence of seizure; n (%)	12 (34.28%)	11 (6.21%)	<0.001	7.873 (3.115-19.898)
Presence of sepsis; n (%)	23 (65.71%)	21 (11.86%)	<0.001	14.238 (6.186-32.766)
Presence of TTNB; n (%)	8 (22.85%)	12 (6.77%)	0.005	4.074 (1.524- 10.885)
Presence of IVH; n (%)	3(8.57%)	2(1.12%)	0.024	8.203 (1.317- 51.059)
Presence of RDS; n (%)	10 (28.57%)	9 (5.08%)	<0.001	7.466 (2.764-20.170)
Presence of NEC; n (%)	3 (8.57%)	2 (1.12%)	0.024	8.203 (1.317-51.059)
Presence of shock; n (%)	6 (17.14%)	2 (1.12%)	<0.001	18.103 (3.484-94.064)

POG-Period of Gestation, SD-Standard Deviation, n-number, ROP-Retinopathy of Prematurity, TTNB-Transient Tachypnea of Newborn, IVH-Intraventricular Hemorrhage, RDS-Respiratory Distress syndrome, NEC-Necrotising Enterocolitis, CI-Confidence Interval

There was no difference in the gestational age and birth weight of late preterm newborn with and without ROP. Mean gestational age of late preterm with ROP was 34.82weeks±0.95weeks, whereas mean gestational age of late preterm without ROP was 35.07weeks±0.84weeks (p-0.117).

Similarly, mean birth weight of late preterm with ROP was 1536.3 gm 1±292.0 gm, whereas mean birth weight of late preterm without ROP was 1609.37g±240.93g (p-0.115). There was significant difference in the duration of oxygen therapy in late preterm newborn with and without ROP (6.657± 2.531days vs 0.694±1.397days, p<0.001).

In an attempt to analyze the risk factors for the development of ROP in late preterm, univariate analysis followed by multivariate or stepwise logistic regression analysis was performed sequentially.

Following risk factors were found to be significant in univariate analysis for the development of ROP in late preterm-use of oxygen, birth asphyxia, sepsis, apnea, anemia, seizure, use of phototherapy, blood transfusion, TTNB, IVH, RDS, NEC and shock (Table 2).

Stepwise logistic regression analysis of the factors found significant in univariate analysis-use of oxygen, duration of oxygen, presence of birth asphyxia and presence of anemia were found to be significant independent risk factors of ROP in late preterm (Table 3).

Table 3: Logistic regression analysis of risk factors of ROP in late preterm newborn.

Risk factors of ROP	P value	Adjusted OR	95% CI
Use of oxygen	0.032	1.475	1.155-3.289
Duration of oxygen therapy	0.012	2.331	1.322-6.327
Presence of birth asphyxia	0.019	1.542	1.143-4.988
Use of Packed red blood cell	0.183	1.021	0.172-5.221
Presence of anemia	0.024	1.212	1.103-3.226
Presence of apnea	0.218	0.347	0.045-9.349
Use of phototherapy	0.418	0.539	0.224-1.297
Presence of seizure	0.612	0.446	0.114-1.740
Presence of sepsis	0.322	1.176	0.314-4.129
Presence of TTNB	0.389	1.691	0.654-4.782
Presence of IVH	0.284	0.814	0.080-8.076
Presence of RDS	0.438	4.686	0.689-9.053
Presence of NEC	0.671	0.689	0.066-7.156
Presence of shock	0.389	1.097	0.342-10.231

ROP-Retinopathy of Prematurity, TTNB-Transient Tachypnea of Newborn, IVH-Intraventricular Hemorrhage, RDS-Respiratory Distress syndrome, NEC-Necrotising Enterocolitis, CI-Confidence Interval

DISCUSSION

Authors have conducted the present study in context of a district level SNCU whereas most of the previous studies concentrated on preterm population in tertiary care NICU. Very few articles have exclusively concentrated on late preterm newborn. Newborns cared in NICU may differ considerably from newborn in SNCU both in terms of disease severity and quality of treatment received. There have been only a few studies in India from SNCU setting so far. Though ROP is mostly a disease of extremely preterm newborn in western countries, it is not so uncommon in more mature and heavier newborns in developing countries.[8,9] ROP has been reported in larger babies with a birth weight between 1500 and 2000 grams.[8] There have been several anecdotal reports from ophthalmologist that ROP has been seen in newborn between 1750 and 2000 gm birth weight. Cerman et al showed that incidence of ROP was 41.4% and therapy was required in 4% preterm in gestational age group of 29-32 weeks, in comparison to preterm of 33-37 weeks gestational age who developed ROP in 18.1% and 0.8% cases had to be treated. Cerman et al concluded that ROP can also occur in more mature newborns.[10] One study from Xian, China have conducted a retrospective analysis in newborn greater than 2 kg birth weight and compared findings with less than 2 kg birth weight population. They came to conclusion that out of all the cases who developed ROP, 9.9 % belonged to high birth weight population (more than 2 kg) and this group constituted 6.3 % of all babies who required treatment. The high birth weight group had no special characteristics in terms of severity and risk factors compared to newborns with lower birth weight.[11] From a physiological viewpoint as retinal vessels mature by 44-45 weeks of gestational age, retinopathy of prematurity can occur in late preterm population. There is insufficient knowledge regarding risk factors, incidence, severity, need for therapy in this subgroup. Zhang Z et al concluded Low birth weight, increasing days of oxygen use and myocardial injury are risk factors for ROP in late preterm newborn.[11] Low gestational age, low birth weight, BPD,NEC have been shown as risk factors of ROP in late preterm by Port et al.[12] Authors have found increasing days of oxygen use, birth asphyxia and anemia to be risk factors of ROP in late preterm. In India National Neonatology Forum guidelines recommend screening of infants less than 34 weeks gestational age or less than 1750 grams birth weight, and 34-36[6/7] weeks gestational age and 1750-2000-gram birth weight if sick. In view of increased incidence of ROP in more mature preterm Jalali et al recommended modification of screening criteria for ROP in India and other middle-income group countries to include entire preterm population.[2] In present study incidence of APROP was 3.30%. Compared to extremely preterm newborns in developed countries, more mature and heavier infants in low-middle income countries are prone to develop APROP especially in the setting of uncontrolled oxygen use, multiple episodes of sepsis and other co morbid risk factors.[13] In present study authors have attempted to analyse incidence and risk factors of ROP in bigger and more mature babies. Confidence interval of some of these risk factors studied were large indicating small number of newborn in different risk groups. As only 41% of variability in ROP can be explained by included risk factors, larger multicentre prospective trial including several district hospital SNCU should be conducted to identify the risk factors associated with ROP in district hospital settings. Several risk factors such as-lack of human milk intake, chorioamnionitis, poor weight gain, presence of BPD which have been found to be associated with ROP could not be assessed in present study as very sick babies were transferred to higher center. The present study has addressed one of the major contributors of recent ROP epidemic in India due to improving survival of preterm at district level SNCU where the standard care for prevention of severe ROP is often lacking. The non-availability of screening facilities, inappropriate knowledge of the disease among caregivers and inadequate information conveyed to the parents has most often complicated the situation. The number newborn lost to follow up visit are alarmingly higher due to lack of tracking and follow up facilities in the district. The data from a single SNCU in West Bengal will reflect the disease burden of all the district level SNCUs in India. The optimization of neonatal care, strict adherence to ROP screening policy and collaboration with nearest tertiary care centre equipped with trained ophthalmologist may help to reduce the potential risk of childhood blindness.

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